TO: Examiner Ziska
FROM: Your searcher (Dilip Pandya, STIC 308-4268)
RE : Ser. No. 07/726,812
Date: Apr 21, 1993

Please note, since there were a considerable no. of hits with medline, no other databases were searched, should you require a modified search, please do not hesitate to contact me.

Also, it may be of interest for you to know that I did a very similar search recently for examiner Larson(A.U 1808) on Ser. No. 07/603,803, you may interested to look at that case.

=> d his

(FILE 'HOME' ENTERED AT 14:24:40 ON 21 APR 93)
SET PAGELENGTH SCROLL

FILE 'MEDLINE' ENTERED AT 14:24:52 ON 21 APR 93
L1 818 S (WEISS S?/AU OR REYNOLDS B?/AU)
L2 36567 S (CELL DIFFERENTIATION)/CT
L3 3984 S (NERVE GROWTH FACTORS)/CT
L4 6532 S (EPIDERMAL GROWTH FACTOR-UROGASTRONE)/CT
L5 56980 S (STEM CELLS+NT)/CT
L6 2 S L1 AND L4
L7 21 S L1 AND (L2 OR L3 OR L4 OR L5)

=> d l7 bib abs hit 3 (AUTHOR SEARCH)

L7 ANSWER 3 OF 21 COPYRIGHT 1993 NLM
AN 93057807 MEDLINE
TI A multipotent EGF-responsive striatal embryonic progenitor cell produces neurons and astrocytes.
AU **Reynolds BA**; Tetzlaff W; **Weiss S**
CS Department of Anatomy, University of Calgary Faculty of Medicine, Alberta, Canada.
SO J Neurosci, (1992 Nov) 12 (11) 4565-74
Journal code: JDF ISSN: 0270-6474
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9302
AB The mitogenic actions of epidermal growth factor (EGF) were examined in low-density, dissociated cultures of embryonic day 14 mouse striatal primordia, under serum-free defined conditions. EGF induced the proliferation of single progenitor cells that began to divide between 5 and 7 d in vitro, and after 13 d in vitro had formed a cluster of undifferentiated cells that expressed nestin, an intermediate filament present in neuroepithelial stem cells. In the continued presence of EGF, cells migrated from the proliferating core and differentiated into neurons and astrocytes. The actions of EGF were mimicked by the homolog transforming growth factor alpha (TGF alpha), but not by NGF, basic fibroblast growth factor, platelet-derived growth factor, or TGF beta. In EGF-generated cultures, cells with neuronal morphology contained immunoreactivity for GABA, substance P, and methionine-enkephalin, three neurotransmitters of the adult striatum. Amplification of embryonic day 14 striatal mRNA by using reverse transcription/PCR revealed mRNAs for EGF, TGF alpha, and the EGF receptor. These findings suggest that EGF and/or TGF alpha may act on a multipotent progenitor cell in the striatum to generate both neurons and astrocytes.

=> d l7 bib abs 4 5 8 10 12 14 16 18

L7 ANSWER 4 OF 21 COPYRIGHT 1993 NLM
AN 92360764 MEDLINE
TI Hypothesis: the target cell of GM-CSF is a macrophage precursor

capable to produce cells with the property to secrete a G-CSF like activity.

AU Mora ML; Santiago E; Montesinos JJ; **Weiss-Steider B**
CS Laboratory of Cellular Differentiation and Cancer, National University of Mexico.)
SO Eur Cytokine Netw, (1992 May-Jun) 3 (3) 337-41
Journal code: A56 ISSN: 1148-5493
CY France (Z1.542.286.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9211
AB The induction of granulocyte and macrophage colony formation by the granulocyte-macrophage colony stimulating factor (GM-CSF) on bone marrow cells (BMC) was evaluated as a function of time in agar cultures. We found that while macrophage cell clusters were very abundant on the first two days of culture, granulocytic cell clusters did not appear until the third day. We also found that macrophage colonies were present from the fourth day of culture, while granulocyte colonies did not appear until the fifth day. When two day cell clusters were transferred to cultures with GM-CSF we observed that only macrophage-colonies developed. On the other hand, when four day clusters were transferred, both granulocyte and macrophage colony formation was obtained in a similar way as the one obtained when using GM-CSF with fresh BMC. Two day clusters did not respond to granulocyte colony stimulating factor (G-CSF) while fourth day clusters generated granulocytic colonies in a similar way as when G-CSF was used with fresh BMC. In order to test the hypothesis that granulocyte colony formation in these assays could be a result of the secretion of G-CSF by the macrophages previously induced by GM-CSF, lysates from macrophage colonies were used to induce colony formation on BMC. We observed that colonies, mainly granulocytic, were induced in a similar way as when G-CSF was used. Finally, the possibility that GM-CSF is just a macrophage inducer with the property to produce cells that secrete G-CSF is discussed.

L7 ANSWER 5 OF 21 COPYRIGHT 1993 NLM
AN 92205351 MEDLINE
TI Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system [see comments]
AU **Reynolds BA; Weiss S**
CM Comment in: Science 1992 Mar 27;255(5052):1646
CS Department of Pathology, University of Calgary Faculty of Medicine, Alberta, Canada.)
SO Science, (1992 Mar 27) 255 (5052) 1707-10
Journal code: UJ7 ISSN: 0036-8075
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9207
AB Neurogenesis in the mammalian central nervous system is believed to end in the period just after birth; in the mouse striatum no new neurons are produced after the first few days after birth. In this study, cells isolated from the striatum of the adult mouse brain were

induced to proliferate in vitro by epidermal growth factor. The proliferating cells initially expressed nestin, an intermediate filament found in neuroepithelial stem cells, and subsequently developed the morphology and antigenic properties of neurons and astrocytes. Newly generated cells with neuronal morphology were immunoreactive for gamma-aminobutyric acid and substance P, two neurotransmitters of the adult striatum in vivo. Thus, cells of the adult mouse striatum have the capacity to divide and differentiate into neurons and astrocytes.

L7 ANSWER 8 OF 21 COPYRIGHT 1993 NLM
AN 90353470 MEDLINE
TI Evidence that G-CSF is a fibroblast growth factor that induces granulocytes to increase phagocytosis and to present a mature morphology, and that macrophages secrete 45-kd molecules with these activities as well as with G-CSF-like activity.
AU Mendoza JF; Caceres JR; Santiago E; Mora LM; Sanchez L; Corona TM; Machuca C; Zambrano IR; Martinez RD; **Weiss-Steider B**
CS Laboratory of Cellular Differentiation and Cancer, Escuela Nacional de Estudios Profesionales Zaragoza, Mexico.)
SO Exp Hematol, (1990 Sep) 18 (8) 903-10
Journal code: EPR ISSN: 0301-472X
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9011
AB Evidence is provided that conditioned medium from a macrophage-like cell line contains molecules of approximately 45 kd molecular weight with granulocyte colony-stimulating factor (G-CSF)-like activity as well as with the property of inducing granulocytes to phagocytose latex particles and to mature morphologically. This type of differentiation was found to be induced on either bone marrow or induced granulocytes, but not on resident or induced macrophages. On the other hand, resident but not induced macrophages are shown to induce these types of activities when challenged by bacterial lipopolysaccharides. Evidence that macrophages produce a factor that is mitogenic for fibroblasts is also provided. This activity was measured by the induction of increased proliferation by either low-density or saturated cultures of fibroblasts. Human recombinant G-CSF was employed and found also to possess these dual capabilities of inducing both the proliferation and differentiation of granulocytes as well as the proliferation of fibroblasts. Finally, a mechanism for the regulation of myeloid cell production and differentiation is described in which G-CSF produced by macrophages not only induces granulocytes to differentiate but induces fibroblasts to proliferate and secrete macrophage colony-stimulating factor (M-CSF), which in turn makes myeloid monocyte precursors proliferate and secrete more G-CSF.

L7 ANSWER 10 OF 21 COPYRIGHT 1993 NLM
AN 89285821 MEDLINE
TI Evidences that fibroblasts and epithelial cells produce a specific type of macrophage and granulocyte inducer, also known as colony-stimulating factor, and that monocyte-macrophages can produce

another factor with proliferative inducing activity on myeloid cells and differentiative activity on macrophages.
AU Zambrano IR; Caceres JR; Mendoza JF; Santiago E; Mora LM; Morales MG; Corona MT; **Weiss-Steider B**
CS Escuela Nacional de Estudios Profesionales Zaragoza, Laboratorio de Diferenciacion Celular y Cancer, UNAM, Mexico D.F.)
SO Ann N Y Acad Sci, (1989) 554 141-55
Journal code: 5NM ISSN: 0077-8923
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8909
AB Molecules with the property to induce proliferation of bone marrow cells in liquid cultures, and with colony-stimulating activity, were found on media conditioned (MC) by lung fibroblasts and kidney epithelial cells. These factors presented an apparent mol wt of 70,000 and 22,000 d respectively. Also when MC by epithelial cells from lungs was tested for the induction of proliferation of bone marrow cells a molecule with 22,000 d was detected. These molecules are thought to be CSF because they induce colony formation, and they are also similar in mol wt to two of the already known CSF. In fact the GM-CSF obtained from endotoxic lungs with a large epithelial cell content has a mot wt of 22,000 d, and the CSF-1 produced by a fibroblast cell line had 70,000. When the MC by fibroblast was used to induce bone marrow cells to proliferate, three new molecules with colony-stimulating activity were secreted. These molecules with apparent mol wts of 45,000, 30,000 and 17,000 d were also found in the MC by bone marrow cells when induced to proliferate with MC by epithelial cells. When the 45,000-d molecules was used in induced bone marrow cells to proliferate, once again the 30,000- and the 17,000-d molecules were secreted. Evidence is also provided that the 45,000-d molecule is produced by the monocyte-macrophage cells, and that it can induce Fc receptors or resident and elicited peritoneal macrophages. The possibility that the production of CSF is cell specific is discussed together with two models to explain the way in which these molecules can participate as proliferative (MGI-1) and differentiative (MGI-2) function in normal myeloid cell differentiation. Finally, a new terminology is proposed to classify this family of molecules.

L7 ANSWER 12 OF 21 COPYRIGHT 1993 NLM
AN 89137317 MEDLINE
TI Evidence that the macrophage-granulocyte inducer (MGI) is produced during cell proliferation, stored in G0, released in G1, cell specific, and induces the secretion of other colony-stimulating activities (CSA).
AU Zambrano IR; Mendoza JF; Caceres JR; Santiago E; Mora LM; Marin TN; **Weiss-Steider B**
CS Escuela Nacional de Estudios Profesionales Zaragoza, Laboratorio de Diferenciacion Celular y Cancer, Mexico D.F.)
SO Exp Hematol, (1989 Mar) 17 (3) 267-72
Journal code: EPR ISSN: 0301-472X
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals; Cancer Journals
EM 8906
AB The secretion of the macrophage and granulocyte inducer (MGI), also known as colony-stimulating factor (CSF), by epithelial cells from lungs and kidneys, and by fibroblasts from lungs, was determined as a function of time in culture; it was found to be secreted during the initial exponential proliferation period, and not when the cells approached saturation density. When the cells were again induced to proliferate, large amounts of CSF were released after 3 h, thus hinting at the existence of a reserve pool. A CSF activity of 70,000 daltons was found in cultures of fibroblasts from lungs, kidneys, and the peritoneal cavity, a 45,000-dalton CSF was obtained from mouse peritoneal macrophages, and from bone marrow cells when activated for macrophage proliferation, and a 22,000-dalton CSF was found from epithelial cells, thus suggesting that the different CSFs are cell specific. When fibroblast CSF was used to induce bone marrow cells, three new molecules with colony-stimulating activity were produced, of 45,000, 30,000, and 17,000 daltons. The fraction with the 17,000-dalton activity also contained interleukin 1 activity, hinting at an indirect induction of colony formation by this factor. Finally the possible existence of a cascade reaction in which one CSF induces the appearance of other CSFs during the normal regulation of myeloid cell differentiation is discussed.

L7 ANSWER 14 OF 21 COPYRIGHT 1993 NLM
AN 87198273 MEDLINE
TI Primary culture of striatal neurons: a model of choice for pharmacological and biochemical studies of neurotransmitter receptors.
AU Bockaert J; Gabrion J; Sladeczek F; Pin JP; Recasens M; Sebben M; Kemp D; Dumuis A; **Weiss S**
SO J Physiol (Paris), (1986) 81 (4) 219-27
Journal code: JRB ISSN: 0021-7948
CY France (Z1.542.286.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8708
AB Striatal neurons were cultured from fetal mouse brain and maintained in serum-free medium for 14-21 days in vitro (DIV). A double coating of culture dishes with polyornithine and fetal calf serum was needed in order to obtain synaptic differentiation. Synaptic vesicles were present in axon terminals as well as in varicosities along extended axons. The presence of differentiated synapses was confirmed by the immunostaining of the preparation with synapsin I antibody. After 13 days in vitro synapsin I was present in axonal varicosities and particularly concentrated at contact points between axonal terminals and postsynaptic sites on adjacent axons or perikarya. On a surface of 429 mm2 on which 2211 cells were observed under phase contrast microscopy only 7% were stained with an antibody against GFAP (glial fibrillary acidic protein). One or two days after the formation of differentiated synapses (11 DIV), a Ca2+-dependent liberation of GABA was observed. These cultures are an excellent model for studying the coupling of some neurotransmitter receptors with an adenylate

cyclase. In particular using this preparation we were able to demonstrate that dopamine (D2) and serotonin-(5-HT1) receptors are negatively coupled with an adenylate cyclase. These cultures are also an excellent model to study the coupling of some neurotransmitter receptors with inositol phosphate producing enzymes. We demonstrated for the first time that the quisqualate subtype of glutamate receptors is able to increase inositol phosphate production in striatal neurons.

L7 ANSWER 16 OF 21 COPYRIGHT 1993 NLM
AN 86177579 MEDLINE
TI Synaptogenesis of cultured striatal neurons in serum-free medium: a morphological and biochemical study.
AU **Weiss S**; Pin JP; Sebben M; Kemp DE; Sladeczek F; Gabrion J; Bockaert J
SO Proc Natl Acad Sci U S A, (1986 Apr) 83 (7) 2238-42
Journal code: PV3 ISSN: 0027-8424
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8607
AB Striatal neurons were cultured from the fetal mouse brain and maintained in serum-free medium for 14-21 days in vitro (DIV). Pretreatment of the culture dishes successively with a polycation followed by fetal calf serum resulted in rapid neuron attachment and neurite proliferation. After 9-10 DIV, electron microscope observations revealed the presence of vesicles in axon terminals forming mature synapses with axons and perikarya of adjacent neurons and in varicosities along extended axons. Synapsin I, a synaptic vesicle-specific protein, was present only in neuronal perikarya after 3 DIV, in perikarya and in varicosities along extended axons after 6 DIV, and in varicosities and contact points between axon terminals and adjacent axons or perikarya after 11-14 DIV. Neurotransmitter-stimulated intracellular formation of cAMP decreased markedly during neuronal differentiation. Inositol phosphate formation in response to neurotransmitters, however, increased significantly throughout the period of striatal neuronal development. K+ (56 mM) depolarization resulted in a 2-fold increase in endogenous gamma-aminobutyric acid (GABA) release from striatal neurons, 50% of which was Ca2+-dependent, between 3 and 11 DIV. Between 11 and 14 DIV, subsequent to synapse formation (as revealed by electron microscope observations), GABA release evoked by 56 mM K+ increased up to 5-fold, 75% of which was Ca2+-dependent. It appears that the complete differentiation of striatal neurons in serum-free medium may provide a suitable model for the study of the physiological and regulatory mechanisms involved in nerve cell development.

L7 ANSWER 18 OF 21 COPYRIGHT 1993 NLM
AN 82135752 MEDLINE
TI Evidence of the existence of a factor that induces Fc receptors on bone marrow cells.
AU Calcagno M; Perez JR; Waldo MG; Cabrera G; **Weiss-Steider B**
SO Blood, (1982 Apr) 59 (4) 756-60
Journal code: A8G ISSN: 0006-4971

CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 8207
AB The existence of a molecule responsible for the induction of Fc receptor (FcR) on bone marrow cells (FcR inducer, FcRI) is demonstrated in conditioned media from the macrophage-like cell line WR19M.1 activated by bacterial lipopolysaccharides. The molecular weight obtained from molecular sieving chromatography in gel and density gradient sedimentation is found to be 18,500 daltons and 16,000 daltons, respectively, with an isoelectric pH of 7.4. The factor is found to be thermolabile and trypsin sensitive. The macrophage and granulocyte inducer (MGI), also known as colony-stimulating factor (CSF) or colony-stimulating activity (CSA), is identified from the same source and found to have a molecular weight and an isoelectric pH different from FcRI. The fractions that contained the MGI did not induce FcR on bone marrow cells, while the fractions rich in FcRI did not induce colony formation.

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=> d que l9;d bib abs 1-6
L4          6532 SEA FILE=MEDLINE (EPIDERMAL GROWTH FACTOR-UROGASTRONE)/CT

L5         56980 SEA FILE=MEDLINE (STEM CELLS+NT)/CT
L8           701 SEA FILE=MEDLINE L4 AND L5
L9             6 SEA FILE=MEDLINE L8 AND (NEURAL OR NEURONAL)


=> d l9 bib ab 1

L9   ANSWER 1 OF 6  COPYRIGHT 1993 NLM
AN  93057807  MEDLINE
TI  A multipotent EGF-responsive striatal embryonic progenitor cell
    produces neurons and astrocytes.
AU  Reynolds BA; Tetzlaff W; Weiss S
CS  Department of Anatomy, University of Calgary Faculty of Medicine,
    Alberta, Canada.)
SO  J Neurosci, (1992 Nov)  12 (11)  4565-74
    Journal code: JDF  ISSN: 0270-6474
CY  United States (Z1.107.567.875.)
DT  Journal; Article; (JOURNAL ARTICLE)
LA  English
FS  Priority Journals
EM  9302
AB  The mitogenic actions of epidermal growth factor (EGF) were examined
    in low-density, dissociated cultures of embryonic day 14 mouse
    striatal primordia, under serum-free defined conditions. EGF induced
    the proliferation of single progenitor cells that began to divide
    between 5 and 7 d in vitro, and after 13 d in vitro had formed a
    cluster of undifferentiated cells that expressed nestin, an
    intermediate filament present in neuroepithelial stem cells. In the
    continued presence of EGF, cells migrated from the proliferating core
    and differentiated into neurons and astrocytes. The actions of EGF
    were mimicked by the homolog transforming growth factor alpha (TGF
    alpha), but not by NGF, basic fibroblast growth factor,
    platelet-derived growth factor, or TGF beta. In EGF-generated
    cultures, cells with neuronal morphology contained
    immunoreactivity for GABA, substance P, and methionine-enkephalin,
    three neurotransmitters of the adult striatum. Amplification of
    embryonic day 14 striatal mRNA by using reverse transcription/PCR
    revealed mRNAs for EGF, TGF alpha, and the EGF receptor. These
    findings suggest that EGF and/or TGF alpha may act on a multipotent
    progenitor cell in the striatum to generate both neurons and
    astrocytes.

=> d l9 bib ab 2-6

L9   ANSWER 2 OF 6  COPYRIGHT 1993 NLM
AN  92107958  MEDLINE
TI  Cytotactin binding: inhibition of stimulated proliferation and
    intracellular alkalinization in fibroblasts.
AU  Crossin KL
CS  Rockefeller University, New York, NY 10021.
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NC DK04256 (NIDDK)
SO Proc Natl Acad Sci U S A, (1991 Dec 15) 88 (24) 11403-7
Journal code: PV3 ISSN: 0027-8424
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9204
AB Cytotactin is an extracellular matrix protein that is dynamically and transiently expressed in a place-dependent fashion during development by glial cells, fibroblasts, and several other cell types. In the present study, the effects of cytotactin on cell proliferation were examined in fibroblastic cells in culture. NIH 3T3 mouse cells plated on tissue culture substrata in the presence of soluble cytotactin remained rounded for longer periods than untreated control cells, similar to their response to cytotactin-coated substrates. These rounding effects could be prevented by pretreatment of the cells with nocodazole, a microtubule-disrupting agent. Cytotactin inhibited the proliferation of fibroblasts in culture in a dose- and time-dependent manner, and this inhibition occurred even after nocodazole treatment. In addition, the presence of cytotactin inhibited proliferation stimulated by growth factors or tumor promoter. These effects on cell growth were accompanied by an early inhibition of the intracellular alkalinization that normally occurs upon mitogenic stimulation by a number of growth-promoting agents. Together these observations suggest that cytotactin is an endogenous cell surface modulatory protein and provide a possible mechanism whereby cytotactin may contribute to pattern formation during development, regeneration, tumorigenesis, and wound healing.

L9 ANSWER 3 OF 6 COPYRIGHT 1993 NLM
AN 92098586 MEDLINE
TI **Neural** cell adhesion molecule mediates contact-dependent inhibition of growth of near-diploid mouse fibroblast cell line m5S/1M.
AU Aoki J; Umeda M; Takio K; Titani K; Utsumi H; Sasaki M; Inoue K
CS Department of Health Chemistry, Faculty of Pharmaceutical Science, University of Tokyo, Japan.)
SO J Cell Biol, (1991 Dec) 115 (6) 1751-61
Journal code: HMV ISSN: 0021-9525
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9204
AB A near-diploid mouse fibroblast cell line m5S/1M used in this study shows a high sensitivity to contact-dependent inhibition of growth, and the addition of EGF causes both morphological change and loss of contact-dependent inhibition of growth. The m5S/1M cell and its transformants obtained by x-ray irradiation have been used to search for the cell surface glycoproteins that are responsible for the growth regulation via cell-cell interactions. Lectin blotting analyses showed that the expression of the cell surface glycoprotein of 140 kD (140KGP) is highly sensitive to the transformation induced either by x-ray irradiation or by the EGF stimulation. We purified

the 140KGP and found that it was composed of two glycoproteins. The major component of 140KGP was identified as **neural** cell adhesion molecule (NCAM) by amino acid sequence analyses of the peptide fragments and by the cross-reactivity with anti-NCAM mAb, clone H28.1.2.3. Monoclonal antibody against 140KGP (clone LN-10) recognizes all three isoforms of NCAM expressed on m5S/1M cell and showed that the expression of NCAM was highly sensitive to the transformation. Furthermore, the immobilized LN-10 strongly inhibited the growth of actively proliferating m5S/1M cells and the LN-10 in a soluble form showed a significant growth-stimulating effect on the confluent quiescent cultures of m5S/1M cells. The results show that NCAM plays a major role in the contact-dependent inhibition of growth of m5S/1M, and that NCAM might be involved in the regulation of cell growth during embryogenesis and formation of nervous systems.

L9 ANSWER 4 OF 6 COPYRIGHT 1993 NLM
AN 91283374 MEDLINE
TI **Neuronal** differentiation in response to epidermal growth factor of transfected murine P19 embryonal carcinoma cells expressing human epidermal growth factor receptors.
AU den Hertog J; de Laat SW; Schlessinger J; Kruijer W
CS Hubrecht Laboratory, Netherlands Institute for Developmental Biology, Utrecht.)
SO Cell Growth Differ, (1991 Mar) 2 (3) 155-64
Journal code: AYH ISSN: 1044-9523
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9110
AB The human epidermal growth factor receptor (hEGF-R) was introduced into murine P19 embryonal carcinoma (EC) cells, which do not express endogenous EGF-R. Undifferentiated stable P19 EC transfectants containing multiple copies of the hEGF-R complementary DNA were isolated. These cells express functional EGF-R, exhibiting characteristic biphasic EGF binding and intrinsic tyrosine protein kinase activity. Whereas normally EGF induces the expression of multiple nuclear protooncogenes, only junB expression is induced by EGF in the HER-transfected cells. This indicates that undifferentiated P19 EC cells contain at least part of a signal transduction machinery capable of coupling to the ectopically expressed hEGF-R. Interestingly, **neuronal** differentiation is induced in these cells in response to EGF under culture conditions resembling those during early preimplantation embryogenesis. These results indicate that **neuronal** differentiation of pluripotent P19 EC cells can be induced via activation of a tyrosine protein kinase signaling pathway.

L9 ANSWER 5 OF 6 COPYRIGHT 1993 NLM
AN 90374499 MEDLINE
TI Growth factor responses of enriched bipotential glial progenitors.
AU Hunter SF; Bottenstein JE
CS Department of Pharmacology-Toxicology, University of Texas Medical Branch, Galveston 77550.
NC NS01228 (NINDS)

NS20375 (NINDS)
SO Brain Res Dev Brain Res, (1990 Jul 1) 54 (2) 235-48
Journal code: DBR ISSN: 0165-3806
CY Netherlands (Z1.542.651.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9012
AB Responses of oligodendrocyte/type 2 astrocyte (O-2A) glial progenitors from neonatal rat brains to different growth factors were studied by a new, serum-free method. Enriched tertiary cultures of O-2A progenitors were produced after 6-7 days in vitro using the growth-promoting factors from the B104 CNS **neuronal** cell line, heparin, and mechanical separation. These cultures contained about 75-90% A2B5+ cells with less than 10% type 1 astrocytes, and the yield was 4.4 x 10(5) cells/brain. B104 conditioned medium (CM) factors increased both O-2A progenitor number and [3H]thymidine-labeling indices after three days. However, type 1 astrocyte CM was required for continued survival of enriched progenitors beyond 1 day in tertiary culture. Platelet-derived growth factor (PDGF) and glia maturation factor also showed growth-promoting action, but were less effective than B104 CM at tested doses. PDGF-neutralizing antibodies had no effect on progenitor survival or response to B104 CM factors. Thus, type 1 astrocyte-derived PDGF was not required for this response, B104 CM is not likely to contain PDGF, and B104 CM factors act directly on O-2A progenitors. Fibroblast growth factor, transforming growth factor beta, interleukin 2, epidermal growth factor, and triiodothyronine showed no growth-promoting activity; moreover, interleukin 2, epidermal growth factor, transforming growth factor beta, and 0.5% fetal bovine serum inhibited B104 CM action. Enriched progenitors exhibited bipotentiality by slowly differentiating into oligodendrocytes in serum-free medium, whereas culture in 10% fetal bovine serum increased type 2 astrocytes. Thus, this new method selects or produces progenitors which are similar to those from mature brains.

L9 ANSWER 6 OF 6 COPYRIGHT 1993 NLM
AN 80218472 MEDLINE
TI Growth factors.
AU Herschman HR; Lusis AJ; Groopman JE
SO Ann Intern Med, (1980 May) 92 (5) 650-62 Ref: 118
Journal code: 5A6 ISSN: 0003-4819
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 8010
AB Humoral regulation of somatic and hematopoietic cell growth has been intensely investigated during the past decade. Growth hormone is unique because it regulates the size of the person within the constraints of the genetic program. The somatomedins and insulin growth factors are low molecular weight polypeptides believed to mediate some functions of growth hormone. Epithelial growth factor and nerve growth factor are well-characterized polypeptides that

influence the growth and differentiation of epithelial and **neural** tissues and interact with specific cell surface receptors. The hematopoietins are a family of polypeptide hormones that specifically regulate the proliferation and differentiation of stem cells giving rise to erythrocytes, granulocytes, monocytes, megakaryocytes, and B and T lymphocytes. Platelet-derived growth factor modulates the proliferation of fibroblasts in vitro and may have a role in the development of atherosclerosis and myelofibrosis. New knowledge on the biochemistry and physiology of growth factors will probably have a substantial impact on our understanding of human diseases involving abnormal cell growth.

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=> d que l13
L2         36567 SEA FILE=MEDLINE (CELL DIFFERENTIATION)/CT
L4          6532 SEA FILE=MEDLINE (EPIDERMAL GROWTH FACTOR-UROGASTRONE)/CT

L12          337 SEA FILE=MEDLINE L2 AND L4
L13           25 SEA FILE=MEDLINE L12 AND (NEURAL OR NEURONAL)

=> d l13 bib ab 1-25

L13  ANSWER 1 OF 25  COPYRIGHT 1993 NLM
AN   93149584  MEDLINE
TI   Adenovirus 5 E1A proteins disrupt the neuronal phenotype
     and growth factor responsiveness of PC12 cells by a conserved region
     1-dependent mechanism.
AU   Boulukos KE; Ziff EB
CS   Howard Hughes Medical Institute, Department of Biochemistry, NYU
     Medical Center, New York 10016.)
SO   Oncogene, (1993 Feb)  8 (2)  237-48
     Journal code: ONC  ISSN: 0950-9232
CY   England: United Kingdom (Z1.542.363.300.)
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals; Cancer Journals
EM   9305
AB   Expression in PC12 cells of adenovirus 5 E1a proteins dramatically
     changes cell morphology and disrupts neuronal
     differentiation. We demonstrate that the nerve growth factor (NGF)
     receptors, p140trk and p75NGFR, as well as the epidermal growth
     factor receptor are undetectable in E1a-expressing PC12 cells. This
     correlates with a repression of mRNAs for the chromaffin- and
     neuronal-specific proteins, tyrosine hydroxylase and
     peripherin, while more ubiquitously expressed genes remain
     unaffected. One possible mechanism of E1a action could thus be the
     repression of a coordinately regulated group of chromaffin- and/or
     neuronal-specific genes. Furthermore, we show taht E1a
     conserved region 1, which binds p105Rb and p300, is necessary for
     this E1a-dependent effect. This indicates that cellular proteins
     interacting with E1a conserved region 1 may be implicated in growth
     arrest, expression of neuron-specific functions and orderly
     differentiation of PC12 cells in response to NGF.

L13  ANSWER 2 OF 25  COPYRIGHT 1993 NLM
AN   93138079  MEDLINE
TI   Epidermal growth factor and transforming growth factor-alpha can
     induce neuronal differentiation of rat pheochromocytoma
     PC12 cells under particular culture conditions.
AU   Nakafuku M; Kaziro Y
CS   DNAX Research Institute of Molecular and Cellular Biology, Palo Alto,
     CA 94304-1104.)
SO   FEBS Lett, (1993 Jan 11)  315 (3)  227-32
     Journal code: EUH  ISSN: 0014-5793
CY   Netherlands (Z1.542.651.)
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
```

FS Priority Journals; Cancer Journals
EM 9304
AB In rat pheochromocytoma PC12 cells, NGF induces **neuronal** differentiation. Upon stimulation with NGF, Ras is activated to a GTP-bound form, and the activated Ras can induce **neuronal** differentiation. Recently, we and others observed that epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha) can also activate Ras in PC12 cells. This is puzzling since previous reports indicated that EGF stimulates proliferation rather than differentiation in PC12 cells. In this paper, we re-examined the biological effect of EGF and TGF-alpha, and found that these factors can also induce **neuronal** differentiation under particular culture conditions. Not only the outgrowth of long neurites, but the induction of neurofilament proteins and the metalloprotease transin was also observed in the EGF- and TGF-alpha-stimulated cells. These data clearly indicate that in addition to NGF, EGF and TGF-alpha can also induce the differentiation of PC12 cells under particular conditions.

L13 ANSWER 3 OF 25 COPYRIGHT 1993 NLM
AN 93098781 MEDLINE
TI Sustained activation of the mitogen-activated protein (MAP) kinase cascade may be required for differentiation of PC12 cells. Comparison of the effects of nerve growth factor and epidermal growth factor.
AU Traverse S; Gomez N; Paterson H; Marshall C; Cohen P
CS Department of Biochemistry, University of Dundee, Scotland, U.K.)
SO Biochem J, (1992 Dec 1) 288 (Pt 2) 351-5
Journal code: 9YO ISSN: 0264-6021
CY England: United Kingdom (Z1.542.363.300.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9303
AB Stimulation of PC12 cells with nerve growth factor (NGF) increased mitogen-activated protein kinase kinase (MAPKK) activity > 20-fold after 5 min to a level that was largely sustained for at least 90 min. MAPKK activity was stimulated to a similar level by epidermal growth factor (EGF), but peaked at 2 min, declining thereafter and returning to basal levels after 60-90 min. Activation of MAPKK by either growth factor occurred prior to the activation of MAP kinase, consistent with MAPKK being the physiological activator of MAP kinase. The results demonstrate that the transient activation of MAPKK by EGF and its sustained activation by NGF underlies the transient and sustained activation of MAP kinase induced by EGF and NGF respectively. NGF or EGF induced the same two forms of MAPKK that were resolved on a Mono Q column. The Peak-1 MAPKK was activated initially and partially converted into the more acidic peak-2 MAPKK after prolonged growth-factor stimulation. The Peak-2 MAPKK was 20-fold more sensitive to inactivation by the catalytic subunit of protein phosphatase 2A. Stimulation with NGF caused a striking translocation of MAP kinase from the cytosol to the nucleus after 30 min, but not nuclear translocation of MAP kinase occurred after stimulation with EGF. The results suggest that sustained activation of the MAP kinase cascade may be required for MAP kinase to enter the nucleus, where it may initiate the gene transcription events required

for **neuronal** differentiation of PC12 cells.

L13 ANSWER 4 OF 25 COPYRIGHT 1993 NLM
AN 93001161 MEDLINE
TI PC12 cell **neuronal** differentiation is associated with prolonged p21ras activity and consequent prolonged ERK activity.
AU Qui MS; Green SH
CS Department of Biology, University of Iowa, Iowa City 52242.
NC NS26538 (NINDS)
SO Neuron, (1992 Oct) 9 (4) 705-17
Journal code: AN8 ISSN: 0896-6273
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9301
AB Expression of oncogenic ras in PC12 cells causes **neuronal** differentiation and sustained protein tyrosine phosphorylation and activity of extracellular signal-regulated kinases (ERKs), p42erk2 and p44erk1. Oncogenic N-ras-induced **neuronal** differentiation is inhibited by compounds that block ERK protein tyrosine phosphorylation or ERK activity, indicating that ERKs are not only activated by p21ras but serve as the primary downstream effectors of p21ras. Treatment of PC12 cells with nerve growth factor or fibroblast growth factor results in **neuronal** differentiation and in a sustained elevation of p21ras activity, of ERK activity, and of ERK tyrosine phosphorylation. Epidermal growth factor, which does not cause **neuronal** differentiation, stimulates only transient (< 1 hr) activation of p21ras and ERKs. These data indicate that transient activation of p21ras and, consequently, ERKs is not sufficient for induction of **neuronal** differentiation. Prolonged ERK activity is required: a consequence of sustained activation of p21ras by the growth factor receptor protein tyrosine kinase.

L13 ANSWER 5 OF 25 COPYRIGHT 1993 NLM
AN 92340486 MEDLINE
TI Phosphatidylinositol 3-kinase is activated by nerve growth factor and epidermal growth factor in PC12 cells.
AU Carter AN; Downes CP
CS Department of Biochemistry, University of Dundee, United Kingdom.)
SO J Biol Chem, (1992 Jul 25) 267 (21) 14563-7
Journal code: HIV ISSN: 0021-9258
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9210
AB The effects of nerve growth factor (NGF) and epidermal growth factor (EGF) on the regulation of phosphatidylinositol 3-kinase (PtdIns 3-kinase) activity were assessed in rat pheochromocytoma (PC12) cells. Both NGF and EGF induced a rapid activation of PtdIns 3-kinase as assessed by a dramatic rise in growth factor-induced PtdIns 3-kinase activity found in antiphosphotyrosine immunoprecipitates. The intracellular levels of two of the lipid products of PtdIns

3-kinase, phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P3) and phosphatidylinositol 3,4-bisphosphate (PtdIns(3,4)P2), also rose dramatically, exhibiting time courses very similar to the appearance of PtdIns 3-kinase in immunoprecipitates. The activation of PtdIns 3-kinase is, therefore, a common event in the signal transduction processes elicited by growth factors stimulating distinct cellular end points in PC12 cells, namely the NGF-induced **neuronal** differentiation and EGF-stimulated mitogenesis. Thus the intracellular products of this enzyme may function in early biochemical events that are common components of the pathways controlling both differentiation and proliferation.

L13 ANSWER 6 OF 25 COPYRIGHT 1993 NLM
AN 92251839 MEDLINE
TI Differentiation of PC12 cells with nerve growth factor is associated with induction of transin synthesis and release.
AU Fillmore HL; Mainardi CL; Hasty KA
CS Department of Anatomy, University of Tennessee, Memphis.
NC AI 22603 (NIAID)
AR 39166 (NIAMS)
SO J Neurosci Res, (1992 Apr) 31 (4) 662-9
Journal code: KAC ISSN: 0360-4012
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9208
AB We have identified and characterized a calcium-dependent metalloproteinase which is induced in rat pheochromocytoma cells (PC12 cells) during differentiation with nerve growth factor (NGF). Assays of proteolytic activity in media from differentiated PC12 cell cultures revealed a NGF-dependent increase in the activity of a proteinase which has a molecular weight of 62 kDa. Studies using serine, thiol, and metalloproteinase inhibitors demonstrated that the secreted enzyme is a metalloproteinase. Treatment of culture supernatants with aminophenylmercuric acid (APMA), a known activator of metalloproteinases, resulted in a decrease in the molecular weight of the proteinase. Western blot analysis of culture media from NGF-treated PC12 cells using an antibody directed against a synthetic peptide of rat transin identified this metalloproteinase as transin. Treatment of PC12 cells with acidic and basic fibroblast growth factor (FGF) resulted in distinct morphological changes as well as transin release. Incubation with epidermal growth factor (EGF) did not induce transin release. Dexamethasone inhibited the induction of transin release by NGF. 35S-methionine labeling and immunoprecipitation of newly synthesized proteins from culture supernatants confirmed that NGF induced the synthesis of this enzyme 8 hr after NGF treatment. The NGF-dependent induction of transin, a calcium-dependent metalloproteinase which degrades type IV collagen, laminin, and fibronectin suggests that transin may function to degrade the surrounding extracellular matrix during the invasive process of axonal elongation in **neuronal** development thereby allowing the movement of growth cones and axons toward specific targets.

L13 ANSWER 7 OF 25 COPYRIGHT 1993 NLM
AN 92240811 MEDLINE
TI Ethanol increases cholinergic and decreases GABAergic **neuronal** expression in cultures derived from 8-day-old chick embryo cerebral hemispheres: interaction of ethanol and growth factors.
AU Brodie C; Vernadakis A
CS Department of Pharmacology, University of Colorado School of Medicine, Denver 80262.
NC AA08626 (NIAAA)
SO Brain Res Dev Brain Res, (1992 Feb 21) 65 (2) 253-7
Journal code: DBR ISSN: 0165-3806
CY Netherlands (Z1.542.651.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9208
AB We have shown that ethanol exposure during embryogenesis affects a variety of parameters of **neuronal** growth both in ovo and in vitro. Moreover, we have found that growth factors significantly attenuate the in ovo neurotoxicity produced by ethanol. In this study, we further examined the direct effects of ethanol exposure on neuron-enriched cultures derived from 8-day-old chick embryo cerebral hemispheres consisting primarily of differentiated neurons. In addition, we examined the interaction of ethanol and nerve growth factor (NGF) or epidermal growth factor (EGF) when the growth factors were given concomitantly with ethanol. Choline acetyltransferase (ChAT) and glutamic acid decarboxylase (GAD) were used as markers for cholinergic and GABAergic **neuronal** phenotypic expression, respectively. We found that ethanol alone enhanced ChAT and reduced GAD activities in a dose-dependent manner. NGF and EGF given alone enhanced the expression of both **neuronal** phenotypes. When NGF was given concomitantly with ethanol at C4-8 the decline in GAD produced by ethanol was reversed. The effects of concomitant administration of ethanol and growth factors on ChAT activity revealed that ethanol interfered with the increases produced by the growth factors and especially with NGF when given alone. We conclude from these findings that ethanol may interfere with **neuronal** phenotypic expression by altering **neuronal** responsiveness to neurotrophic signals important for **neuronal** differentiation.

L13 ANSWER 8 OF 25 COPYRIGHT 1993 NLM
AN 92198727 MEDLINE
TI Effects of growth factors on the differentiation of **neural** crest cells and **neural** crest cell-derivatives.
AU Hall BK; Ekanayake S
CS Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canada.)
SO Int J Dev Biol, (1991 Dec) 35 (4) 367-87 Ref: 331
Journal code: AV3 ISSN: 0214-6282
CY Spain (Z1.542.846.)
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English
FS Priority Journals
EM 9207
AB During neurulation, **neural** crest cells migrate to many regions of the body to give rise to a wide variety of cell types. Many premigratory **neural** crest cells are pluripotent, their potency for differentiation being gradually restricted as they migrate along definite pathways and interact with factors present in the microenvironment. Effects of growth factors on these cells have been discussed in the present review. Mediation of growth factors in differentiation varies with the cell type. Growth factors exert a direct influence on the differentiation of **neural** and other related **neural** crest-derived tissues such as endocrinal tissues but evidence for such influences on **neural** crest-derived mesenchymal tissues is limited. For example, NGF, BDNF, and other factors present in **neural** tube extracts and glioma cell conditioned medium are essential for the differentiation of sensory neurons. Similarly, NGF, insulin, IGFs and possibly other undescribed factors are necessary for the differentiation of sympathetic neurons. IGFs also enhance the proliferation of mesenchymal derivatives of both **neural** crest and mesodermal origin. Glucocorticoid-mediated differentiation of **neural** crest-derived chromaffin endocrine cells that are ontogenetically closely related to sympathetic neurons can be inhibited by NGF, and chromaffin cells can be induced to express the **neuronal** phenotype by NGF. Some growth factors, such as NGF, act on **neural** crest- and not on placodally-derived neurons, whether the former are sensory or sympathetic. Placodal sensory neurons possess NGF receptors, but only display a limited response to NGF, perhaps because of low affinity of the receptors. Other growth factors, such as BDNF, selectively act upon sensory neurons, whether **neural** crest- or placodally-derived. Although extracellular matrix products play a role in initiating the differentiative process, signals from growth factors are necessary for the establishment of the functionally competent phenotype of **neural** crest-derived neurons, a situation that does not apply for **neural** crest-derived mesenchymal cells. It is interactions with ECM components deposited by epithelia that govern the differentiation of mesenchymal derivatives. Growth factors do effect proliferation of mesenchymal derivatives and inhibit mesenchymal differentiation. Although direct involvement of single growth factors in transformation o f one mesenchymal phenotype to another has not been reported so far, their localization at sites of epithelial-mesenchymal interactions in palate teeth and mandible, and the ability of excess growth factors to interrupt normal development is suggestive of their possible involvement. One group of growth factors, BMPs, can influence differentiation of cartilage, including those of **neural** crest origin.(ABSTRACT TRUNCATED AT 400 WORDS)

L13 ANSWER 9 OF 25 COPYRIGHT 1993 NLM
AN 92011917 MEDLINE
TI ras isoprenylation is required for ras-induced but not for NGF-induced **neuronal** differentiation of PC12 cells.
AU Qiu MS; Pitts AF; Winters TR; Green SH

CS Department of Biology, University of Iowa, Iowa City 52242.
NC NS26538 (NINDS)
MH14629 (NIMH)
SO J Cell Biol, (1991 Nov) 115 (3) 795-808
Journal code: HMV ISSN: 0021-9525
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9201
AB We have used compactin, an inhibitor of mevalonate biosynthesis, to block p21ras posttranslational modification and membrane association in PC12 cells. Previous studies have demonstrated a requirement for isoprenylation for mitogenic effects of activated p21ras in mammalian cells and for function of RAS gene products in yeast. Immunoprecipitation of [35S]methionine-labeled p21ras from PC12 cell homogenates confirmed that the processed p21ras species is missing from compactin-treated PC12 cells. Immunoprecipitation from particulate and cytosolic fractions of PC12 cells confirmed that compactin blocks p21ras membrane association: p21ras is confined to the cytosol fraction. Induction of **neuronal** differentiation and ornithine decarboxylase (ODCase) transcription by oncogenic p21N-ras does not occur in compactin-treated cells indicating that activity of oncogenic p21N-ras expressed in PC12 cells is abolished by compactin treatment. Thus, p21ras isoprenylation or association with the membrane appears to be required for early responses and **neuronal** differentiation attributable to p21ras activation. In contrast, blockade of p21ras isoprenylation and membrane association by compactin treatment did not significantly reduce PC12 cell responses to NGF. Responses examined included rapid phosphorylation of tyrosine hydroxylase, rapid induction of ODCase expression, survival in serum-free medium and **neuronal** differentiation. Compactin blocked growth factor-induced rapid changes in cell surface morphology but did so whether this response was induced by NGF or by EGF. These results indicate that functional p21ras is not necessary for responses to NGF which in turn implies that if a ras-dependent NGF signal transduction pathway exists, as has been previously suggested, at least one additional ras-independent pathway must also be present.

L13 ANSWER 10 OF 25 COPYRIGHT 1993 NLM
AN 91283374 MEDLINE
TI **Neuronal** differentiation in response to epidermal growth factor of transfected murine P19 embryonal carcinoma cells expressing human epidermal growth factor receptors.
AU den Hertog J; de Laat SW; Schlessinger J; Kruijer W
CS Hubrecht Laboratory, Netherlands Institute for Developmental Biology, Utrecht.)
SO Cell Growth Differ, (1991 Mar) 2 (3) 155-64
Journal code: AYH ISSN: 1044-9523
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9110

AB The human epidermal growth factor receptor (hEGF-R) was introduced into murine P19 embryonal carcinoma (EC) cells, which do not express endogenous EGF-R. Undifferentiated stable P19 EC transfectants containing multiple copies of the hEGF-R complementary DNA were isolated. These cells express functional EGF-R, exhibiting characteristic biphasic EGF binding and intrinsic tyrosine protein kinase activity. Whereas normally EGF induces the expression of multiple nuclear protooncogenes, only junB expression is induced by EGF in the HER-transfected cells. This indicates that undifferentiated P19 EC cells contain at least part of a signal transduction machinery capable of coupling to the ectopically expressed hEGF-R. Interestingly, **neuronal** differentiation is induced in these cells in response to EGF under culture conditions resembling those during early preimplantation embryogenesis. These results indicate that **neuronal** differentiation of pluripotent P19 EC cells can be induced via activation of a tyrosine protein kinase signaling pathway.

L13 ANSWER 11 OF 25 COPYRIGHT 1993 NLM
AN 91212976 MEDLINE
TI Chimeric NGF-EGF receptors define domains responsible for **neuronal** differentiation.
AU Yan H; Schlessinger J; Chao MV
CS Department of Cell Biology and Anatomy, Cornell University Medical College, New York, NY 10021.)
SO Science, (1991 Apr 26) 252 (5005) 561-3
Journal code: UJ7 ISSN: 0036-8075
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9108
AB To determine the domains of the low-affinity nerve growth factor (NGF) receptor required for appropriate signal transduction, a series of hybrid receptors were constructed that consisted of the extracellular ligand-binding domain of the human epidermal growth factor (EGF) receptor (EGFR) fused to the transmembrane and cytoplasmic domains of the human low-affinity NGF receptor (NGFR). Transfection of these chimeric receptors into rat pheochromocytoma PC12 cells resulted in appropriate cell surface expression. Biological activity mediated by the EGF-NGF chimeric receptor was assayed by the induction of neurite outgrowth in response to EGF in stably transfected cells. Furthermore, the chimeric receptor mediated nuclear signaling, as evidenced by the specific induction of transin messenger RNA, an NGF-responsive gene. Neurite outgrowth was not observed with chimeric receptors that contained the transmembrane domain from the EGFR, suggesting that the membrane-spanning region and cytoplasmic domain of the low-affinity NGFR are necessary for signal transduction.

L13 ANSWER 12 OF 25 COPYRIGHT 1993 NLM
AN 91105576 MEDLINE
TI Stimulatory effects of retinal extract and fibroblast growth factor on lentoidogenesis in cultures of chick embryo neuroretinal cells.
AU Karim SA; de Pomerai DI

CS Department of Biology, Faculty of Science, King Abdul Aziz University, Jeddah, Saudi Arabia.)
SO Cell Differ Dev, (1990 Sep) 31 (3) 169-76
Journal code: CDD ISSN: 0922-3371
CY Ireland (Z1.542.467.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9105
AB A crude extract prepared from embryonic chick retina stimulates growth and particularly transdifferentiation into lens when added as a supplement to neuroretinal (NR) cultures in vitro. This effect is especially marked when using a medium (H) containing 5% horse serum, where growth factors are likely to be limiting. The level of delta-crystallin (lens marker) production in such cultures increases with the concentration of extract. Using extracts from earlier and later stages of retinal development, there is an age-dependent decline in the extent to which transdifferentiation is stimulated. However, such extracts have little effect on the activity of CAT, a **neuronal** marker enzyme. These effects are most probably mediated by growth factors present in the retinal extract acting upon Muller glial cells or their precursors in the NR cultures. In support of this suggestion, we show that purified fibroblast growth factor (but not epidermal growth factor) exerts similar effects on both culture growth and delta-crystallin accumulation.

L13 ANSWER 13 OF 25 COPYRIGHT 1993 NLM
AN 90374499 MEDLINE
TI Growth factor responses of enriched bipotential glial progenitors.
AU Hunter SF; Bottenstein JE
CS Department of Pharmacology-Toxicology, University of Texas Medical Branch, Galveston 77550.
NC NS01228 (NINDS)
NS20375 (NINDS)
SO Brain Res Dev Brain Res, (1990 Jul 1) 54 (2) 235-48
Journal code: DBR ISSN: 0165-3806
CY Netherlands (Z1.542.651.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9012
AB Responses of oligodendrocyte/type 2 astrocyte (O-2A) glial progenitors from neonatal rat brains to different growth factors were studied by a new, serum-free method. Enriched tertiary cultures of O-2A progenitors were produced after 6-7 days in vitro using the growth-promoting factors from the B104 CNS **neuronal** cell line, heparin, and mechanical separation. These cultures contained about 75-90% A2B5+ cells with less than 10% type 1 astrocytes, and the yield was 4.4 x 10(5) cells/brain. B104 conditioned medium (CM) factors increased both O-2A progenitor number and [3H]thymidine-labeling indices after three days. However, type 1 astrocyte CM was required for continued survival of enriched progenitors beyond 1 day in tertiary culture. Platelet-derived growth factor (PDGF) and glia maturation factor also showed growth-promoting action, but were less effective than B104 CM at tested doses.

PDGF-neutralizing antibodies had no effect on progenitor survival or response to B104 CM factors. Thus, type 1 astrocyte-derived PDGF was not required for this response, B104 CM is not likely to contain PDGF, and B104 CM factors act directly on O-2A progenitors. Fibroblast growth factor, transforming growth factor beta, interleukin 2, epidermal growth factor, and triiodothyronine showed no growth-promoting activity; moreover, interleukin 2, epidermal growth factor, transforming growth factor beta, and 0.5% fetal bovine serum inhibited B104 CM action. Enriched progenitors exhibited bipotentiality by slowly differentiating into oligodendrocytes in serum-free medium, whereas culture in 10% fetal bovine serum increased type 2 astrocytes. Thus, this new method selects or produces progenitors which are similar to those from mature brains.

L13 ANSWER 14 OF 25 COPYRIGHT 1993 NLM
AN 90373471 MEDLINE
TI Attenuation of neurotoxicity following anoxia or glutamate receptor activation in EGF- and hippocampal extract-treated **neuronal** cultures.
AU Pauwels PJ; van Assouw HP; Leysen JE
CS Department of Biochemical Pharmacology, Janssen Research Foundation, Beerse, Belgium.)
SO Cell Signal, (1989) 1 (1) 45-54
Journal code: AVB ISSN: 0898-6568
CY England: United Kingdom (Z1.542.363.300.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9012
AB Neurotoxicity following anoxia or glutamate receptor activation was studied in primary **neuronal** cultures grown in serum-free, chemically defined CDM R12 medium. Exposure to 1 mM KCN, 0.5 mM kainic acid and 0.5 mM N-methyl-D-aspartate led to progressive **neuronal** degeneration. This damage was quantified by measuring lactate dehydrogenase released in the culture medium. The toxic effects were observed early during the development of the **neuronal** culture (from 4 days in vitro on) and seemed to be neuron-specific since astrocyte cultures were not affected. Chronic treatment of the **neuronal** cultures with epidermal growth factor at 10 ng/ml and hippocampal extract at dil. 1/833 (w/v) induced morphological alterations, increased beta-adrenergic receptor coupled adenylate cyclase activity, increased level of total lactate dehydrogenase activity in the case of epidermal growth factor-treated cultures, and attenuation of lactate dehydrogenase release following exposure to KCN or glutamate receptor agonists. The alterations observed are probably due to the proliferation and differentiation of glial cells in these treated cultures. This suggests that glial cells protect neurons in vitro from degeneration induced by anoxia or glutamate receptor activation.

L13 ANSWER 15 OF 25 COPYRIGHT 1993 NLM
AN 90354884 MEDLINE
TI Differential effects of NGF, FGF, EGF, cAMP, and dexamethasone on neurite outgrowth and sodium channel expression in PC12 cells.
AU Pollock JD; Krempin M; Rudy B

CS Division of Biology, California Institute of Technology, Pasadena 91125.
NC 2F 32 NS07903-03 (NINDS)
GM26976 (NIGMS)
NS21327 (NINDS)
SO J Neurosci, (1990 Aug) 10 (8) 2626-37
Journal code: JDF ISSN: 0270-6474
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9011
AB PC12 cells are a pheochromocytoma cell line that can be made to differentiate into sympatheticlike neurons by nerve growth factor (NGF). An essential component of the NGF-induced differentiation is the development of action potentials and sodium channels. Using whole-cell clamp we have confirmed that NGF produces a 5- to 6-fold increase in sodium channel density. The sodium channels induced by NGF are not different from those in cells not treated with NGF and are similar to those in other cell types. Basic fibroblast growth factor (FGF), another growth factor that causes PC12 cells to differentiate into sympathetic-like neurons, also produces a 5- to 6-fold increase in sodium current density with channels indistinguishable from those in PC12 cells treated and not treated with NGF. Basic FGF produces the same or somewhat larger increase in sodium channel density but much less neurite outgrowth. In contrast, epidermal growth factor does not produce neurite outgrowth but induces a small, reproducible increase in sodium channel density. Cyclic AMP produces spike-like processes but not neurites and results in a decrease in sodium current and sodium current density. Dexamethasone, a synthetic glucocorticoid, inhibits the increase in sodium current and sodium current density but does not antagonize the neurite outgrowth induced by NGF. Thus, although the increase in sodium channel expression induced by NGF and basic FGF parallels the changes in morphology that lead to neurite outgrowth, it clearly does not depend on them. The results show that different aspects of remain
unknown. To address these issues, we used a fully defined **neuronal** cell culture system derived from embryonic rat sympathetic ganglia (DiCicco-Bloom, E., and I. B. Black. 1988. Proc.

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=> d l13 bib ab 16-25

L13 ANSWER 16 OF 25 COPYRIGHT 1993 NLM
AN 90277725 MEDLINE
TI Neuroblast mitosis in dissociated culture: regulation and relationship to differentiation.
AU DiCicco-Bloom E; Townes-Anderson E; Black IB
CS Department of Neurology, Cornell University Medical College, New York 10021.
NC HD 23315 (NICHD)
NS 10259 (NINDS)
EY 06135 (NEI)
+

SO J Cell Biol, (1990 Jun) 110 (6) 2073-86
Journal code: HMV ISSN: 0021-9525
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9009
AB Although neuron generation is precisely regulated during ontogeny, little is known about underlying mechanisms. In addition, relationships between precursor proliferation and the apparent sequence of developmental processes, including cell migration, neurite elaboration, transmitter expression and synaptogenesis remain unknown. To address these issues, we used a fully defined **neuronal** cell culture system derived from embryonic rat sympathetic ganglia (DiCicco-Bloom, E., and I. B. Black. 1988. Proc. Natl. Acad. Sci. USA. 85:4066-4070) in which precursors enter the mitotic cycle. We now find that, in addition to synthesizing DNA, neuroblasts also underwent division in culture, allowing analysis of developmental relationships and mitotic regulation. Our observations indicate that mitotic neuroblasts expressed a wide array of neuron-specific characteristics including extension of neuritic processes with growth cones, elaboration of neurotransmitter enzyme, synthesis and transport of transmitter vesicles and organization of transmitter release sites. These data suggest that neuroblasts in the cell cycle may simultaneously differentiate. Consequently, the apparent sequence of ontogenetic processes is not an immutable, intrinsic **neuronal** program. How, then, are diverse developmental events coordinated? Our observations indicate that neuroblast mitosis is regulated by a small number of epigenetic factors, including insulin and EGF. Since these signals also influence other processes in developing neurons, epigenetic regulation normally may synchronize diverse ontogenetic events.

L13 ANSWER 17 OF 25 COPYRIGHT 1993 NLM
AN 90203060 MEDLINE
TI Potentiation of oncogenic N-ras-induced neurite outgrowth and ornithine decarboxylase activity by phorbol dibutyrate and protein kinase inhibitor H-8.
AU Trotta RJ; Thomson TM; Lacal JC; Pellicer A; Burstein DE
CS Department of Pathology, New York University School of Medicine, New York 10016.
NC NS21648 (NINDS)
CA01025 (NCI)
CA36327 (NCI)
+
SO J Cell Physiol, (1990 Apr) 143 (1) 68-78
Journal code: HNB ISSN: 0021-9541
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9007
AB A recombinant N-ras oncogene, under the transcriptional control of a corticosteroid-inducible mouse mammary tumor virus (MMTV) promoter, has been stably transfected into a PC12 rat pheochromocytoma subline.

This cell line, designated UR61, undergoes N-ras-induced neurite outgrowth and cessation of division when treated with dexamethasone (Guerrero et al.: Biochemical and Biophysical Research Communications 150:1185-1192, 1988). We have employed the UR61 cell line as a model for ras oncogene-induced **neuronal** differentiation. In UR61 cells, dexamethasone-induced expression of the recombinant N-ras gene resulted in time-dependent expression of ornithine decarboxylase enzyme (ODC) activity. Prompted by recent reports of possible functional (Lacal et al.: Molecular and Cellular Biology 7:4146-4149, 1987; Wolfman and Macara: Nature 325: 359-361, 1987) and direct (Jeng et al.: Biochemical and Biophysical Research Communications 145:782-788, 1987) interactions between oncogene ras-coded p21 and protein kinase C (PK-C; Ca++/phospholipid-dependent protein kinase), we employed the protein kinase inhibitor H-8 (N-[2-(methylamino)ethyl]-5-isoquinoline sulfonamide dihydrochloride) and phorbol 12,13-dibutyrate (PDBu) to investigate this putative interaction in the UR61 cells, where ODC activity and neurite outgrowth were used as indicators of oncogenic N-ras action. Treatment of UR61 cells with PDBu depleted cells of PK-C and failed to promote neurite outgrowth but enhanced N-ras-induced neurite outgrowth and ODC activity. H-8, which suppressed ODC induction by forskolin and phorbol myristate acetate, enhanced both N-ras-induced ODC activity and neurite outgrowth. Inhibition of ODC activity by difluoromethylornithine (DFMO) did not suppress oncogenic ras-induced neurite outgrowth, suggesting that these two ras-triggered events are mechanistically independent. These findings suggest that certain actions of N-ras can occur in cells depleted of PK-C, and thus, the role of PK-C in ras-induced differentiation differs from its role in ras-induced mitogenesis and transformation.

L13 ANSWER 18 OF 25 COPYRIGHT 1993 NLM
AN 90180479 MEDLINE
TI NGF induction of the gene encoding the protease transin accompanies **neuronal** differentiation in PC12 cells.
AU Machida CM; Rodland KD; Matrisian L; Magun BE; Ciment G
CS Department of Cell Biology and Anatomy, Oregon Health Sciences University, Portland 97201.)
NC CA 48643
CA 39360
CA 47404
+
SO Neuron, (1989 Jun) 2 (6) 1587-96
Journal code: AN8 ISSN: 0896-6273
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9006
AB Various proteases have been found to be released by the growth cones of developing neurons in culture and have been hypothesized to play a role in the process of axon elongation. We report here that nerve growth factor (NGF) induced the gene encoding the metalloprotease transin in PC12 cells with a time course coincident with the initial appearance of neurites by these cells. Acidic and basic fibroblast growth factors also stimulated transin mRNA expression and neurite

outgrowth, whereas various other agents had no effects on either of these phenomena. In contrast, dexamethasone was found to inhibit the induction of transin mRNA when added with, or following, NGF treatment. Finally, we show that sequences contained within 750 bp of the 5' untranscribed region of the transin gene confer responsiveness to NGF and dexamethasone.

L13 ANSWER 19 OF 25 COPYRIGHT 1993 NLM
AN 90006734 MEDLINE
TI Structure and distribution of the Notch protein in developing Drosophila [published erratum appears in Genes Dev 1989 Dec;3(12A):2020]
AU Kidd S; Baylies MK; Gasic GP; Young MW
CS Howard Hughes Medical Institute, Rockefeller University, New York, New York 10021.)
SO Genes Dev, (1989 Aug) 3 (8) 1113-29
Journal code: FN3 ISSN: 0890-9369
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9001
AB Antibodies to Notch show that it is a stable, high-molecular-weight transmembrane glycoprotein, with epidermal growth factor (EGF)-like elements exposed on the cell surface. The protein is phosphorylated variably on serines of the cytoplasmic domain. Individual Notch polypeptide chains appear to be associated with one another by disulfide bonds, suggesting that homotypic interaction of these proteins is required for function. Immunocytochemistry has revealed striking features of Notch expression that might clarify its function: Cells of the ventral neurogenic ectoderm become conspicuously labeled with the protein prior to embryonic neurogenesis, and Notch appears to be associated with cells destined for both **neural** and epidermal lineages. High levels of Notch become restricted to neuroblasts as they delaminate from the embryonic ectoderm and are apposed to mesoderm. Mesodermal cells express Notch also, suggesting a possible involvement in neurogenesis, or an unknown role in mesoderm differentiation. In larvae and pupae, a correlation of expression and neuroblast mitotic activity is seen for many cells. Notch produced by a dividing neuroblast may persist on derivative cells, including terminally differentiated neurons and nerve processes. In the larval eye imaginal disk, strong Notch expression appears in the morphogenetic furrow, uniformly on cell surfaces as they cluster to form ommatidia. Expression persists on ommatidia after release from the furrow. These patterns suggest a role for Notch in position-dependent development in both initiation and maintenance of cell-surface interactions. In the eye and embryonic ectoderm, uniform expression on cells interacting to produce different developmental lineages from a single primordium suggests that Notch alone may not be sufficient to elaborate cell fates.

L13 ANSWER 20 OF 25 COPYRIGHT 1993 NLM
AN 89231521 MEDLINE
TI Influence of epidermal growth factor on the maturation of fetal rat

brain cells in aggregate culture. An immunocytochemical study.
AU Monnet-Tschudi F; Honegger P
CS Institut de Physiologie, Faculte de Medecine, Universite de Lausanne, Switzerland.)
SO Dev Neurosci, (1989) 11 (1) 30-40
Journal code: EC5 ISSN: 0378-5866
CY Switzerland (Z1.542.883.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8908
AB Maturation of astrocytes, neurons, and oligodendrocytes was studied in serum-free aggregating cell cultures of fetal rat telencephalon by an immunocytochemical approach. Cell type-specific immunofluorescence staining was examined by using antibodies directed against glial fibrillary acidic protein (GFAP) and vimentin, two astroglial markers; neuron-specific enolase (NSE) and neurofilament (NF), two **neuronal** markers, and galactocerebroside (GC), an oligodendroglial marker. It was found that the cellular maturation in aggregates is characterized by distinct developmental increases in immunoreactivity for GFAP, vimentin, NSE, NF, and GC, and by a subsequent decrease of vimentin-positive structures in more differentiated cultures. These findings are in agreement with observations in vivo, and they corroborate previous biochemical studies of this histotypic culture system. Treatment of very immature cultures with a low dose of epidermal growth factor (EGF, 5 ng/ml) enhanced the developmental increase in GFAP, NSE, NF and GC immunoreactivity, suggesting an acceleration of **neuronal** and glial maturation. In addition, EGF was found to alter the cellular organization within the aggregates, presumably by influencing cell migration.

L13 ANSWER 21 OF 25 COPYRIGHT 1993 NLM
AN 86077850 MEDLINE
TI Epidermal growth factor, but not nerve growth factor, stimulates tyrosine-specific protein-kinase activity in pheochromocytoma (PC12) plasma membranes.
AU Boonstra J; van der Saag PT; Feijen A; Bisschop A; de Laat S
SO Biochimie, (1985 Oct-Nov) 67 (10-11) 1177-83
Journal code: A14 ISSN: 0300-9084
CY France (Z1.542.286.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8604
AB Rat pheochromocytoma (PC12) cells contain specific plasma membrane receptors for both epidermal growth factor (EGF) and nerve growth factor (NGF). Whereas EGF addition to PC12 cells causes a persistent enhancement of proliferation. NGF addition induces a transient stimulation of growth, followed by growth arrest and **neuronal** differentiation. Despite these differences in biological response, EGF and NGF share a number of early receptor-mediated responses, which are likely te be related to their effect on cell proliferation. In this paper we show that EGF, but not NGF, is able to stimulate the phosphorylation of membrane proteins. In addition, EGF was able to

stimulate phosphorylation of a synthetic peptide (RR-SRC) by PC12 membranes in a concentration-dependent manner. Kinetic analysis of the phosphorylation reaction indicated that EGF increased the Vmax from 13 to 70 pmoles/min/mg protein, while no change was observed in Km. Furthermore, EGF was able to stimulate tyrosine phosphorylation of angiotensin I and II, to the same extent as RR-SRC. In contrast no effects of NGF on peptide phosphorylation by PC12 membranes were observed. Cross-linking experiments demonstrated the presence of receptors for both NGF and EGF in PC12 membranes. These different effects of NGF and EGF on activation of membrane-associated protein-kinase activity demonstrate that NGF might be able to stimulate growth transiently without stimulating protein kinase activity.

L13 ANSWER 22 OF 25 COPYRIGHT 1993 NLM
AN 83265803 MEDLINE
TI Loss of EGF binding and cation transport response during differentiation of mouse neuroblastoma cells.
AU Mummery CL; van der Saag PT; de Laat SW
SO J Cell Biochem, (1983) 21 (1) 63-75
Journal code: HNF ISSN: 0730-2312
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8311
AB Mouse neuroblastoma cells (clone N1E-115) differentiate in culture upon withdrawal of serum growth factors and acquire the characteristics of neurons. We have shown tht exponentially growing N1E-115 cells possess functional epidermal growth factor (EGF) receptors but that the capacity for binding EGF and for stimulation of DNA synthesis is lost as the cells differentiate. Furthermore, in exponentially growing cells, EGF induces a rapid increase in amiloride-sensitive Na+ influx, followed by stimulation of the (Na+-K+)ATPase, indicating that activation of the Na+/H+ exchange mechanism in N1E-115 cells [1] may be induced by EGF. The ionic response is also lost during differentiation, but we have shown that the stimulation of both Na+ and K+ influx is directly proportional to the number of occupied receptors in all cells whether exponentially growing or differentiating, thus only indirectly dependent on the external EGF concentration. The linearity of the relationships indicates that there is no rate-limiting step between EGF binding and the ionic response. Our data would suggest that as neuroblastoma cells differentiate and acquire **neuronal** properties, their ability to respond to mitogens, both biologically and in the activation of cation transport processes, progressively decreases owing to the loss of the appropriate receptors.

L13 ANSWER 23 OF 25 COPYRIGHT 1993 NLM
AN 83257683 MEDLINE
TI Is epidermal growth factor a modulator of nervous system function?
AU Herschman HR; Goodman R; Chandler C; Simpson D; Cawley D; Cole R; de Vellis J
NC GM 24797
SO Birth Defects, (1983) 19 (4) 79-94

Journal code: A6V ISSN: 0547-6844
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8311

L13 ANSWER 24 OF 25 COPYRIGHT 1993 NLM
AN 83257643 MEDLINE
TI **Neuronal** differentiation in cultured **neural** crest cells: the effect of serum on neurite outgrowth.
AU Ziller C; Le Douarin NM
SO Birth Defects, (1983) 19 (4) 251-61
Journal code: A6V ISSN: 0547-6844
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8311

L13 ANSWER 25 OF 25 COPYRIGHT 1993 NLM
AN 83238662 MEDLINE
TI Ionic responses and growth stimulation induced by nerve growth factor and epidermal growth factor in rat pheochromocytoma (PC12) cells.
AU Boonstra J; Moolenaar WH; Harrison PH; Moed P; van der Saag PT; de Laat SW
SO J Cell Biol, (1983 Jul) 97 (1) 92-8
Journal code: HMV ISSN: 0021-9525
CY United States (Z1.107.567.875.)
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8310
AB Rat pheochromocytoma cells (clone PC12) respond to nerve growth factor (NGF) by the acquirement of a phenotype resembling **neuronal** cells. In an earlier study we showed that NGF causes an increase in Na+,K+ pump activity, as monitored by ouabain-sensitive Rb+ influx. Here we show that addition of epidermal growth factor (EGF) to PC12 cells resulted in a stimulation of Na+,K+ pump activity as well. The increase of Na+,K+ pump activity by NGF or EGF was due to increased Na+ influx. This increased Na+ influx was sensitive to amiloride, an inhibitor of Na+,H+ exchange. Furthermore, no changes in membrane potential were observed upon addition of NGF or EGF. Amiloride-sensitive Na+,H+ exchange in PC12 cells was demonstrated by H+ efflux measurements and the effects of weak acids on Na+ influx. These observations suggest that both NGF and EGF activate an amiloride-sensitive, electroneutral Na+,H+ exchange mechanism in PC12 cells. These findings were surprising in view of the opposite ultimate biological effects of NGF and EGF, e.g., growth arrest vs. growth stimulation. However, within 24 h after addition, NGF was found to stimulate growth of PC12 cells, comparable to EGF. In the presence of amiloride, this stimulated growth by NGF and EGF was abolished. In contrast, amiloride did not affect NGF-induced neurite outgrowth of PC12 cells. From these observations it is concluded that in PC12 cells: (a) NGF has an initial growth

stimulating effect; (b) neurite outgrowth is independent of increased amiloride-sensitive Na+ influx; and (c) growth stimulation by NGF and EGF is associated with increased amiloride-sensitive Na+ influx.